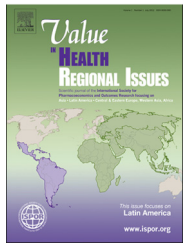
VALUE IN HEALTH REGIONAL ISSUES 8C (2015) 36–42

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/vhri



Cost-Effectiveness and Cost-Utility Analyses of Dabigatran Compared with Warfarin in Patients with Nonvalvular Atrial Fibrillation and Risk Factors for Stroke and Systemic Embolism within Brazilian Private and Public Health Care Systems Perspectives

Camila Pepe Ribeiro de Souza, MsC[1,*], *Natália Bolzachini Santoni, BsC*[2], *Thais Gomes de Melo, MsC*[2], *Marcio Jansen de Oliveira Figueiredo, PhD*[3], *Francisco Carlos da Costa Darrieux, PhD*[4], *Leopoldo Soares Piegas, PhD*[5], *Sheila Ouriques Martins, PhD*[6]

[1]*MedInsight Decisions Health Care, São Paulo, SP, Brazil;* [2]*Boehringer Ingelheim, São Paulo, SP, Brazil;* [3]*State University of Campinas, UNICAMP, Campinas, SP, Brazil;* [4]*Heart Institute InCor, São Paulo, SP, Brazil;* [5]*Dante Pazzanese Institute, São Paulo, SP, Brazil;* [6]*Clinical Hospital of Porto Alegre Porto Alegre, RS, Brazil*

ABSTRACT

Objective: To analyze the cost-effectiveness and cost-utility of dabigatran compared with warfarin in patients with nonvalvular atrial fibrillation with moderate to high risk of ischemic stroke or systemic embolism and eligible for treatment with anticoagulants. **Methods:** Markov-based economic analysis was performed to estimate treatment costs and outcomes. Epidemiological and efficacy data were determined after a critical revision of the medical literature. Unit costs were taken from Brazilian official databases. Only direct medical costs were covered. Costs and benefits were discounted at a rate of 5% per year. Outcomes were expressed as life-year (LY) and quality-adjusted life-year (QALY). **Results:** Dabigatran use is cost-effective in terms of LY and QALY considering a willingness-to-pay threshold of 3 times gross domestic product per capita of 2010 (Brazilian real 57,048/US $24,275.74) per LY and QALY saved in both analyzed perspectives (private and public health care systems). **Conclusions:** Dabigatran use improves patient survival and quality of life compared with warfarin. This represents the best therapeutic option in terms of cost and effectiveness in the prevention of ischemic stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Keywords: stroke prevention, atrial fibrillation, cost-effectiveness, cost-utility, dabigatran.

Introduction

Atrial fibrillation (AF) is a supraventricular arrhythmia in which an atrial electrical activity disorder occurs, causing the atria to lose their ability to contract, not generating atrial systole [1]. In population studies, AF is an important risk factor for ischemic stroke (IS), heart failure, and death [2], with a 3% to 6% annual risk of thromboembolic complications, which is 5 to 7 times greater than the risk in controls with a sinus rhythm [3].

The prevalence of AF is influenced by age, sex, presence of cardiovascular disease, such as valvular disease, and risk factors such as hypertension, diabetes, obesity, and insulin resistance [1,4]. Brazilian data show an annual incidence below 0.1% in the population younger than 40 years and 1.5% and 2.0% in men and women, respectively, older than 80 years [1].

More than 20% of all ISs are attributable to AF [4], thus representing the largest single cause and one of the most important risk factors for the occurrence of this condition in Brazil. The incidence of IS in patients with nonvalvular atrial fibrillation (NVAF) averages 5% per year [5].

AF is related to greater stroke severity, higher mortality, worse functional prognosis after stroke, greater recurrence, and longer hospital stays, resulting in larger and more significant costs to health care systems [6].

To reduce all these risks associated with AF, it is essential to rationally institute an anticoagulant therapy. Currently, therapy with vitamin K antagonists, especially warfarin, is the medication of choice for primary and secondary stroke prevention, transient ischemic attack, and other thromboembolic events in patients with AF at high risk for these events. This therapy, however, has

Conflict of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

* Address correspondence to: Camila Pepe Ribeiro de Souza, MedInsight Decisions Health Care, Av Adolfo Pinheiro, 2058, 5° andar, Alto da Boa Vista, São Paulo Brazil.

E-mail: camila.pepe@gruporesulta.com.br

2212-1099$36.00 – see front matter

http://dx.doi.org/10.1016/j.vhri.2015.02.003

a risk of bleeding events [7]. Therefore, there is an imminent need to establish new anticoagulant agents that are effective, safe, and more convenient to use.

Dabigatran etexilate is a small molecule that is rapidly absorbed after oral administration and converted into dabigatran acting directly by inhibiting thrombin, responsible for the conversion of fibrinogen into fibrin during coagulation cascade and preventing the development of thrombus (clot). In addition, dabigatran has proven its efficacy and safety without the need of coagulation monitoring and dose adjustments, and does not cause dietary restrictions for patients [8].

The objective of the present study was to determine the cost-effectiveness and cost-utility of the use of the new oral anticoagulant dabigatran compared with warfarin in patients with NVAF at risk for IS or systemic embolism and eligible for anticoagulant therapy.

Methods

Target Population

The modeled patient population comprised adults with NVAF at risk for IS or systemic embolism, eligible for treatment with an anticoagulant on the basis of CHADS and CHADSVASc scores. The CHADS2 score is a measure of the risk of stroke in which congestive heart failure, hypertension, an age of 75 years, and diabetes mellitus are each assigned 1 point and previous stroke or transient ischemic attack is assigned 2 points; the score is calculated by summing all the points for a given patient. The mean CHADS2 score in the model was 2.1. Of patients who entered the model, 63.6% were men aged 71 years, considering the predominant prevalence of AF in this age group, according to population-based studies [9].

Study Perspective

This study was developed from the perspectives of the Brazilian private health care system (Sistema de Saúde Suplementar [SSS]) and public health care system (Sistema Único de Saúde [SUS]).

Model Structure

Markov models have two components: structure and parameters. The "structure" refers to health states represented in the model and the possible transitions between them. The "parameters" of the model include the probabilities assigned to transitions between states of health.

To estimate costs and outcomes of each treatment, a Markov model was designed to follow patients with NVAF at risk for clinically relevant events along the natural course of the disease until the end of their lives. This model considered patients transition through different health states, as shown in Fig. 1. The primary and recurrent clinical events included were IS, hemorrhagic stroke, transient ischemic attack (TIA), systemic embolism (SE), acute myocardial infarction (AMI), intracranial hemorrhage (ICH), extracranial hemorrhage, and death. Figure 1 represents the Markov model structure with the health states considered in the analysis.

The model was evaluated within lifetime horizon (10 years). Costs and outcomes were discounted to the present value at a rate of 5% yearly, according to recommendations of the Methodological Guidelines for Economic Studies Evaluation in Health Technology Assessment, published by the Ministry of Health [10].

Patients transition through several health states has considered relevant clinical events such as IS or ICH. Depending on the event severity, patients may either return to the state they were in before the event or suffer a permanent deterioration toward a worse dependence level. In addition, patients can die as a result of a stroke or hemorrhage, or other comorbidities. A 3-month cycle duration was chosen because of the low probability for patients to have more than one severe event within this period, and it reflects the typical duration of temporary treatment discontinuation due to severe hemorrhages.

The modeling analysis allows predicting clinical and economic outcomes for a cohort of 1000 eligible patients over their lifetime, by calculating the life-years (LYs), quality-adjusted life-years (QALYs), and costs accumulated over this period depending on treatment choice. LYs are calculated on the basis of average time (in years) the patient remained alive in the model. QALY

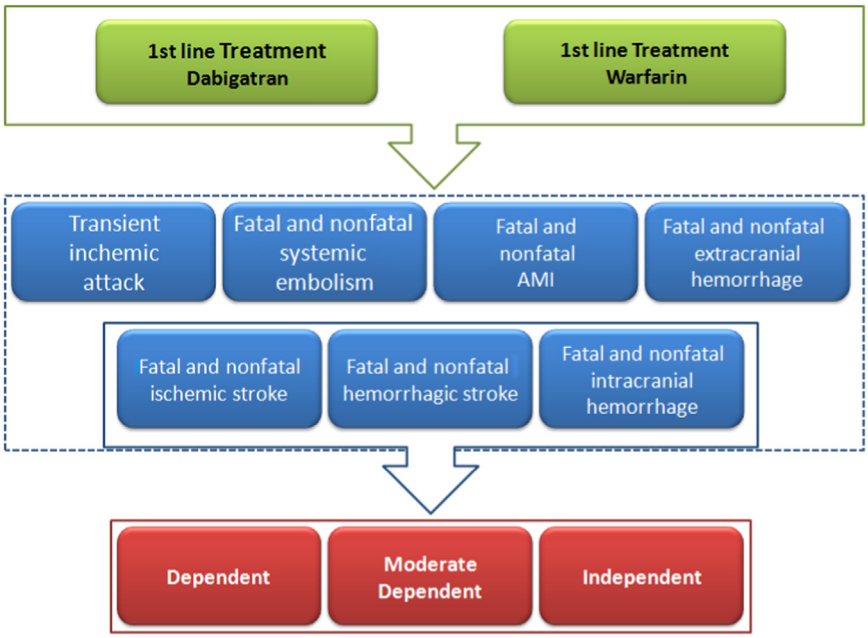


Fig. 1 – Markov model structure.

Table 1 – Treatment lines.

Comparison	First-line treatment	Second-line treatment
Dabigatran vs. warfarin Perspective: SSS	Dabigatran	Acetylsalicylic acid + clopidogrel
	Warfarin	Acetylsalicylic acid + clopidogrel
Dabigatran vs. warfarin Perspective: SUS	Dabigatran	Acetylsalicylic acid
	Warfarin	Acetylsalicylic acid

SSS, Sistema de Saúde Suplementar; SUS, Sistema Único de Saúde.

was estimated by multiplying the time spent in each health state and the corresponding utility for that state (where a utility of 1 denotes full health and 0 denotes death).

Comparators

The treatments considered for patients with NVAF with risk of IS or SE were as follows.

First-line treatment

1. Dabigatran 150 mg twice a day for patients younger than 80 years and dabigatran 110 mg twice a day for patients older than 80 years and
2. warfarin 5 mg/d.

Second-line treatment

1. Acetylsalicylic acid in monotherapy 162 mg/d within the SUS perspective;
2. Acetylsalicylic acid 162 mg/d combined with clopidogrel 75 mg/d within the SSS perspective.

It is worth mentioning that such medicines were used as second-line treatment because this was the Brazilian clinical practice when the current economic analysis was carried out.

Table 1 presents first- and second-line treatments considered in each comparison carried out herein.

Clinical and Safety Data

The economic model was mainly based on two studies: RE-LY [11] and Roskell's meta-analysis [12].

The model considered the risk of events (IS, SE, TIA, ICH, and AMI) related to the treatment with warfarin. Risks concerning the comparison of warfarin with the other analyzed treatment methods (dabigatran used as first-line therapy and acetylsalicylic acid combined or not with clopidogrel used as second-line therapy) were also applied. The risk of each event related to the treatment with warfarin is presented in Table 2.

Relative risks concerning the comparison of warfarin with other analyzed treatment methods are presented in Table 3. Acetylsalicylic acid and acetylsalicylic acid associated with clopidogrel were also analyzed because these drugs were administered after the failure of warfarin or dabigatran as second-line therapy. It is noteworthy that on SUS, acetylsalicylic acid associated with clopidogrel is not incorporated for NVAF indication; for this reason, the second-line treatment on SUS is composed of only acetylsalicylic acid.

Probabilities to develop a permanent or temporary disability (described as independent, moderate dependent, and totally dependent) after an event (IS) for each treatment method are represented in Table 4. This table also presents the probability of mortality within up to 90 days after the event for each treatment.

The risks of fatal SE, fatal extracranial hemorrhage, and fatal acute myocardial infarction considered in the model were 0.46%, 0.03%, and 1.11% per year, respectively [13]. This risk is the same for both treatments (dabigatran and warfarin).

Resources Use and Treatment Costs

On a conservative basis, only direct medical costs were considered. Indirect costs related to patient productivity loss were not included in the analysis.

Resources used for the treatment of acute events and the follow-up of such patients after the event were defined on the basis of specialists' opinion. Medical visits, hospitalizations, laboratory tests, procedures, and drugs were taken into account (for model costs, see Appendix I in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.02.003).

For the perspective of the private health care system, costs of medical visits, laboratory tests, and procedures were obtained through the Brazilian Hierarchical Classification of Medical Procedures (Classificação Brasileira Hierarquizada de Procedimentos Médicos) and the daily hospital stay cost was extracted from the Programa de Estudos Avançados em Administração Hospitalar e de Sistemas de Saúde Bulletin (PROAHSA) [14,15].

For the perspective of the public health care system, these costs were extracted from the public Brazilian database (SIGTAP: Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS) [16].

All costs were collected in 2010 (base year). Total costs were calculated by multiplying the amount of used resources by the unit cost of the respective resources. The costs of each event considered in the model are given in Table 5. For price conversion, from Brazilian real (R$) to US dollar (US $), the average exchange tax published by Central Bank of Brazil, from the last 60 business days to the date of this report elaboration (October 2014) (US $1.00 equals R$ 2.35), was used.

Drugs' unit costs were taken from the Brazilian official database (Câmara de Regulação do Mercado de Medicamentos), considering the ex-factory price added by 18% of value added tax [17]. Prices of drugs used in monthly economic models are given in Table 6.

Table 2 – Risk of event related to warfarin treatment (rate per 100 patients/y).

Risk of ischemic stroke	
$CHADS\ score_2$	
0	0.62
1	0.79
2	0.88
3	1.55
4	1.55
5	2.77
6	2.77
Risk of systemic embolism	0.15
Risk of transient ischemic attack	0.73
Risk of intracranial hemorrhage (hemorrhagic transformation after ischemic stroke)	0.35
Risk of hemorrhagic stroke	0.33
Risk of extracranial hemorrhage	2.71
Risk of acute myocardial infarction	0.59

Source: RE-LY Steering Committee and Investigators and Mixed treatment Comparison [8,9].

Table 3 – Relative risk: Treatment regimens versus warfarin.

Events	RR	95% CI lower	95% CI higher
Ischemic stroke			
Dabigatran	0.80	0.60	1.06
Acetylsalicylic acid + clopidogrel*	2.07	1.38	3.11
Acetylsalicylic acid*	1.62	0.99	2.65
Systemic embolism			
Dabigatran	0.74	0.34	1.61
Acetylsalicylic acid + clopidogrel*	3.57	1.52	8.36
Acetylsalicylic acid*	1.77	0.66	4.77
Transient ischemic attack			
Dabigatran	0.82	0.58	1.15
Acetylsalicylic acid + clopidogrel*	1.56	0.86	2.83
Acetylsalicylic acid*	1.56	0.86	2.83
Intracranial hemorrhage (hemorrhagic transformation after ischemic stroke)			
Dabigatran	0.43	0.21	0.88
Acetylsalicylic acid + clopidogrel*	0.53	0.19	1.45
Acetylsalicylic acid*	0.51	0.16	1.60
Hemorrhagic stroke			
Dabigatran 150mg (twice a day)	0.23	0.09	0.47
Dabigatran 110mg (twice a day)	0.23	0.07	0.91
Acetylsalicylic acid + clopidogrel*	0.84	0.06	5.24
Acetylsalicylic acid*	0.84	0.20	1.53
Extracranial hemorrhage			
Dabigatran	1.05	0.83	1.33
Acetylsalicylic acid + clopidogrel*	1.10	0.71	1.72
Acetylsalicylic acid*	1.14	0.47	2.73
Acute Myocardial infarction			
Dabigatran	1.30	0.92	1.85
Acetylsalicylic acid + clopidogrel*	1.48	0.83	2.63
Acetylsalicylic acid*	1.42	0.84	2.39

Source: Based on RE-LY Steering Committee and Investigators and Mixed treatment Comparison [8,9].
RR, relative risk; CI, Confidence interval.
* Used as second-line treatment.

Sensitivity Analysis

The quantification of uncertainty involved in the economic model and the identification of variables mostly affecting such uncertainty are crucial to support decision making. A probabilistic sensitivity analysis was carried out to validate the results of this evaluation through the use of distributions, instead of the parameter values used in the mathematical model, to establish the impact of uncertainty of each parameter included in the study.

All costs included in the analyses were varied by ±10% considering gamma distributions. Beta distributions were used for transition probabilities, as well as efficacy and safety data. In the probabilistic analysis, 1000 simulations (Monte Carlo second order) were estimated for each perspective and for each outcome. Results were evaluated and ranked as follows: quadrant 1 (incremental effectiveness > 0 and incremental cost > 0), quadrant 2 (incremental effectiveness < 0 and incremental

Table 4 – State of the patient with ischemic stroke and intracranial hemorrhage (rate of 100 patients/y).

Level of disability	Dabigatran 150 mg (twice a day)	Dabigatran 110 mg (twice a day)	Warfarin	Acetylsalicylic acid*	Acetylsalicylic acid + clopidogrel*
Ischemic stroke (%)					
Independent	58.0	32.6	53.9	51.4	53.9
Moderate dependent	14.9	39.9	19.7	18.0	19.7
Totally dependent	4.1	0.1	4.3	6.7	4.3
Mortality in 90 d	22.9	27.3	22.2	23.8	22.2
Intracranial hemorrhage (hemorrhagic transformation after ischemic stroke and hemorrhagic stroke) (%)					
Independent	7.8	7.8	7.8	15.1	15.1
Moderate dependent	8.8	8.8	8.8	16.3	16.3
Totally dependent	31.8	31.8	31.8	42.8	42.8
Mortality in 90 d	51.6	51.6	51.6	25.9	25.9

Source: RE-LY Steering Committee and Investigators [8,9].
* Used as second-line treatment.

Table 5 – Annual cost of clinical events.

Event	Cost			
	SUS		SSS	
Fatal ischemic stroke	R$ 11,809.68	US $5,025.40	R$ 24,625.12	US $10,478.77
Ischemic stroke, independent	R$ 2,811.67	US $1,196.46	R$ 4,327.33	US $1,841.42
Ischemic stroke, moderate disability	R$ 4,469.65	US $1,901.98	R$ 16,447.50	US $6,998.94
Ischemic stroke, totally dependent	R$ 6,280.25	US $2,672.45	R$ 22,982.60	US $9,779.83
Fatal embolism	R$ 11,809.68	US $5,025.40	R$ 24,625.12	US $10,478.77
Nonfatal embolism	R$ 11,809.68	US $5,025.40	R$ 24,625.12	US $10,478.77
Transient ischemic attack	R$ 1,808.29	US $769.49	R$ 3,334.82	US $1,419.07
Fatal intracranial hemorrhage	R$ 15,571.62	US $6,626.22	R$ 22,848.98	US $9,722.97
Fatal hemorrhagic stroke	R$ 23,259.54	US $ 9,897.68	R$ 42,618.19	US $ 18,135.40
Hemorrhagic stroke, independent	R$ 2,811.67	US $1,196.46	R$ 4,327.33	US $184,141.70
Hemorrhagic stroke, moderate disability	R$ 4,469.65	US $1,901.98	R$ 16,447.50	US $6,998.94
Hemorrhagic stroke, totally independent	R$ 6,280.25	US $2,672.45	R$ 22,982.60	US $9,779.83
Fatal extracranial hemorrhage	R$ 1,017.89	US $433.14	R$ 2,958.41	US $1,258.90
Minor bleeding	R$ 19.30	US $8.21	R$ 91.64	US $39.00
Fatal acute myocardial infarction	R$ 15,530.13	US $6,608.57	R$ 37,775.73	US $16,074.78
Nonfatal acute myocardial infarction	R$ 16,852.38	US $7,171.23	R$ 41,983.67	US $17,865.39

Source: Specialist panel, SIGTAP, CBHPM, and PROAHSA [11–13].
CBHPM, Classificação Brasileira Hierarquizada de Procedimentos Médicos; PROAHSA, Programa de Estudos Avançados em Administração Hospitalar e de Sistemas de Saúde SIGTAP, Sistema de Gerenciamento da Tabela de Procedimentos, Medicamentos e OPM do SUS; SSS, Sistema de Saúde Suplementar; SUS, Sistema Único de Saúde.

cost > 0), quadrant 3 (incremental effectiveness < 0 and incremental cost < 0), and quadrant 4 (incremental effectiveness > 0 and incremental cost < 0).

Results

Cost-Effectiveness and Cost-Utility Analysis

Outcomes and total costs were calculated for a lifetime horizon (10 years). Table 7 presents effectiveness results: LY and QALY as well as total costs throughout the time horizon.

Cost-effectiveness results were expressed in terms of incremental cost per LY and QALY gained and are also given in Table 7.

In both perspectives, analyzed results indicate that treatment with dabigatran is associated with a total cost higher than treatment with warfarin. Regarding the outcomes analyzed, dabigatran shows gains in terms of overall survival and quality of life.

Considering a threshold equal to 3 times the gross domestic product (GDP) per capita of 2010 per QALY gained, results indicate that the use of dabigatran is cost-effective compared with the treatment with warfarin (3 × GDP per capita = R$ 57.048) in both perspectives evaluated [18].

Clinical results are different in both perspectives because the second-line treatment considered is different depending on the perspective analyzed (SUS: acetylsalicylic acid; SSS: acetylsalicylic acid combined with clopidogrel).

Thus, dabigatran treatment has been shown to be cost-effective compared with warfarin treatment, with better clinical results and an additional cost justified by the benefit in terms of overall survival and quality of life provided to the patient.

Sensitivity Analysis

After varying all costs involved in the analysis by ±10% by using gamma distributions and transition probabilities, as well as efficacy and safety data by using beta distributions, the conducted probabilistic sensitivity analysis has verified results found in the base-case scenario (see Appendix II in Supplemental Materials found at http://dx.doi.org/10.1016/j.vhri.2015.02.003).

Within the SUS perspective, the sensitivity analysis showed that in 9991 cases the treatment with dabigatran was more effective, with a higher cost, than the treatment with warfarin (quadrant 1). Only in 9 cases, treatment with dabigatran was less effective, with a higher cost, than treatment with warfarin (quadrant 2). From the results presented, considering a threshold equal to 3 times the GDP per capita of 2010 per LY saved, we can consider the drug cost-effective.

Within the SSS, the sensitivity analysis showed that in 9994 cases the treatment with dabigatran was more effective, with a higher cost, than the treatment with warfarin (quadrant 1). Only in 6 cases, treatment with dabigatran was less effective, with

Table 6 – Drug cost items.

Drug	Description	Ex-factory price 18%		Drug presentation
Dabigatran	Pradaxa 110 and 150 mg	R$ 191.14	US $81.34	60 units of 110 and 150 mg
Warfarin	Coumadin 5 mg	R$ 24.53	US$ 10.44	30 units of 5 mg
Acetylsalicylic acid*	Bufferin Cardio 81 mg	R$ 7.83	US$ 3.33	30 units of 81 mg
Clopidogrel*	Plavix 75 mg	R$ 228.31	US$ 97.15	28 units of 75 mg

Source: CMED, Câmara de Regulação do Mercado de Medicamentos—December/2010 [14].
* Used as second-line treatment.

Table 7 – Cost-effectiveness results.

	Perspective: SUS			
	Dabigatran		Warfarin	
Cost				
Total cost	R$ 28,342.91	US $12,060.81	R$ 16,310.37	US $6,940.58
Drugs cost	R$ 15,762.74	US $ 6,707.55	R$ 1,951.22	US $830.31
Events cost	R$ 4,030.31	US $1,715.03	R$ 4,828.38	US $2,054.63
Follow-up cost	R$ 8,549.87	US $3,638.24	R$ 9,530.77	US $4,055.65
Incremental cost			R$ 12,032.54	US 5,120.23
Outcome				
Life-years	9.42		9.11	
Incremental life-years			0.30	
QALY	7.25		6.91	
Incremental QALY			0.35	
ICER				
Per life-year saved			R$ 39,741	US $16,911
Per QALY gained			R$ 34,867	US $14,837
	Perspective: SSS			
	Dabigatran		Warfarin	
Cost				
Total cost	R$ 44,594.87	US $18,976.54	R$ 36,980.32	US $15,736.31
Drugs cost	R$ 18,551.05	US $7,894.06	R$ 5,996.78	US $2,551.82
Events cost	R$ 9,767.99	US $4,156.59	R$ 11,539.30	US $4,910.34
Follow-up costs	R$ 16,275.83	US $6,925.89	R$ 19,444.25	US $8,274.15
Incremental cost			R$ 7,614.55	US $3,240.23
Outcome				
Life-years	9.40		9.10	
Incremental life-years			0.30	
QALY	7.24		6.89	
Incremental QALY			0.34	
ICER				
Per life-year saved			R$ 25,252	US $10,745
Per QALY gained			R$ 22,160	US $9,430

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; SSS, Sistema de Saúde Suplementar; SUS, Sistema Único de Saúde.

a higher cost, than treatment with warfarin (quadrant 2). Considering a threshold equal to 3 times the GDP per capita of 2010 per LY saved, we can say that dabigatran is very cost-effective.

Discussion/Conclusions

Efficacy results were taken from randomized clinical trials and systematic reviews with dabigatran and warfarin in the AF treatment, aiming to establish the impact of different treatments on the prevention of stroke and mortality.

Because of the chronic nature of NVAF, patients are treated on a continuous basis for their entire lives, except for specific causes of discontinuation. Particularly, patients who have undergone an ICH or hemorrhagic stroke discontinue the use of anticoagulants permanently. Patients who have undergone an extracranial hemorrhage may continue the treatment, discontinue the use of anticoagulants temporarily, or discontinue the treatment permanently.

The incidence of clinical events can lead to 1) changes in the treatment (e.g., change in treatment or permanent or temporary treatment discontinuation); 2) changes in a patient's dependence level on a caregiver owing to the stroke and ICH (independent, moderate, or totally dependent); and 3) changes in the risk of future events.

Within the private health care system perspective, treatment with dabigatran is cost-effective compared with that with warfarin, considering a threshold equal to 3 times Brazil's GDP per capita per QALY. Within the public health care system's perspective, results prove that the use of dabigatran is also cost-effective in terms of QALY gained compared with the use of warfarin.

These results were validated through the sensitivity analysis, which points out the inexistence of a major variance in results, even when the limit values were tested for parameters set as important for the result of this economic evaluation.

It is important to emphasize that results shown herein are aligned with other cost-effectiveness evaluations of dabigatran already performed and published for other countries. For example, Kamel et al. [19] have performed a Markovian economic decision model within the perspective of the US private health care system by using clinical data from the RE-LY clinical trial and concluded that the additional cost of the use of dabigatran etexilate amounted to US $9000, resulting, therefore, in an incremental cost-effectiveness ratio (ICER) of US $25,000/QALY [19]. A similar study carried out in Canada found that the ICER of dabigatran etexilate was CAN $10,440 per QALY versus warfarin as per the Canadian health care system perspective [20]. A study performed to access the situation in Sweden has concluded that dabigatran was considered cost-effective for the Swedish health care system, and its ICER (7742 euro per QALY) was lower than the willingness-to-pay value normally accepted in that country [21]. A study recently carried out in Argentina has found that dabigatran is cost-effective with

an incremental cost of ARS 5923 and an ICER of ARS 12,040 per QALY saved.

Premises are known to be required for the elaboration of economic evaluations and likely to have a significant impact on the result. Because of the lack of data about the real world, however, such premises are required and important to develop analyses that could help decision makers take the most assertive decision by choosing the most cost-effective therapeutic option. This limitation is inherent to economic evaluations and is minimized with the application of sensitivity analysis. Among the limitations of this study we have the extrapolation of clinical studies data to lifetime, and the use of specialists' opinion to fulfill the lack of real-world database information on the management of treatment's adverse events. The model used direct costs only, and possible variation in the results if indirect cost is to be added can be hypothesized.

Health economic analyses are effective tools to support health decision makers and Brazilian Unified Health System financers to use resources in the most effective way. The contribution of this economic model, which has used local costs and national medical NVAF treatment guidelines, is to aid decision makers in the task of choosing the best drug strategy for the prevention of stroke and SE in patients with NVAF.

Source of financial support: Boehringer Ingelheim do Brasil supported this study.

Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.vhri.2015.02.003 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Zimerman LI, Fenelon G, Martinelli Filho M, et al. Sociedade Brasileira de Cardiologia. Diretrizes Brasileiras de Fibrilação Atrial. Arq Bras Cardiol 2009;92(6, Suppl.1):1–39.
[2] Benjamin EJ, D'Agostino RB, Wolf PA, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 1998;98:946–52.
[3] Kimura K, Minematsu K, Yamaguchi T. Atrial fibrillation as a predictive factor for severe stroke and early death in 15 831 patients with acute ischaemic stroke. J Neurol Neurosurg Psychiatry 2005;76:679–83.
[4] National Institute for Health and Clinical Excellence. Final scope for the appraisal of dabigatran etexilate for the prevention of stroke and systemic embolism in people with atrial fibrillation. March 2010. Available from: http://www.nice.org.uk/nicemedia/live/12225/47875/47875.pdf. [Accesed April 19, 2011].
[5] Fuster V, Ryden LE, Asinger RW, et al.; Task Force on Practice Guidelines, American College of Cardiology/American Heart Association; Committee for Practice Guidelines, European Society of Cardiology; European Heart Rhythm Association; Heart Rhythm Society. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (writing Committee to revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J 2006;27:1979–2030.
[6] Lip GYH. Atrial fibrillation and mortality. Eur Heart J 1999;20:1525–7.
[7] Lin PJ. Reviewing the reality: why do we need to change. Eur Heart J 2005;7:e15–20.
[8] Ellis CR, Kaiser DW. The clinical efficacy of dabigatran etexilate for preventing stroke in atrial fibrillation patients. Vasc Health Risk Manag 2013;9:341–52.
[9] Chugh SS, Blackshear JL, Win-Kuang S, et al. Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol 2001;37:371–8.
[10] Brasil, Ministério da Saúde, Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Ciência e Tecnologia, Diretrizes metodológicas: Estudos de Avaliação Econômica de Tecnologias em Saúde. Available from: http://200.214.130.94/rebrats/publicacoes/AVALIACAOECONOMICA.pdf [Accessed January 5th, 2011].
[11] Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139–51. Erratum in: N Engl J Med 2010;363:1877.
[12] Roskell NS, Lip GYH, Noack H, et al. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. Thromb Haemost 2010;104:1106–15.
[13] Fang MC, Go AS, Chang Y, et al. Death and disability from warfarin-associated intracranial and extracranial hemorrhages. Am J Med 2007;120:700–5.
[14] Classificação Brasileira Hierarquizada de Procedimentos Médicos. Available from: www.amb.org.br. [Accessed January day, 2011].
[15] PROAHSA-57. Available from: www.hcnet.usp.br/proahsa. [Accessed April 12th, 2011].
[16] Sistema de Gerenciamento da Tabela de Procedimentos. Available from: http://sigtap.datasus.gov.br/tabela-unificada/app/sec/inicio.jsp. [Accessed January 5th, 2011].
[17] Câmara de Regulação do Mercado de Medicamentos. Available from: www.anvisa.org.br. [Accessed December 16th, 2010].
[18] Instituto brasileiro de geografia e estatística (IBGE). Produto Interno Bruto (PIB). Available from: http://www.ibge.gov.br/home/presidencia/noticias/noticia_visualiza.php?id_noticia=1830&id_pagina=1]. [Accessed February 10th, 2011].
[19] Kamel H, Claiborne Johnston S, Donald Easton J, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke 2012;43:881–3.
[20] Sorensen SV, Kansal AR, Connolly S, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. Thromb Haemost 2011;105:1–12.
[21] Davidson T, Husberg M, Janzon M, et al. Cost-effectiveness of dabigatran compared with warfarin for patients with atrial fibrillation in Sweden. Eur Heart J 2013;34:177–83.